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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

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01/04/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/23/10, 8/23/10, 10/18/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. No claims have been amended or added with applicant's response filed October 18, 2010.

2. Claims 42-53, 59-69, 71-73, and 75-80 are under examination.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on April 23, 2010, August 23, 2010, and October 18, 2010 were filed after the mailing date of the non-final office action on April 16, 2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner and an initialed copy of the IDS is included with the mailing of this office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 42-53, 59-69, 71-73, and 75-80 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

Applicant's arguments filed October 18, 2010 have been carefully considered by the examiner but they are deemed not to be persuasive. The response states that, the invention relates to the discovery that immunostimulatory CpG oligonucleotides produce a systemic immune response in a subject that is useful in the treatment of cancer. The pattern of immune response elicited by CpG oligonucleotides exemplified in the specification is predictive of the claimed class of molecules with respect to the treatment of cancer. In fact, it had been known prior to the invention that certain types of infections and bacterial extracts trigger immune responses that can cause regression of cancers. It was the present invention that linked the immune stimulatory effects of bacterial DNA with the presence of unmethylated CpG motifs. One further aspect of the invention is the recognition that a similar type of immune response is triggered by unmethylated CpG motifs as that which is triggered by using bacterial DNA. From this discovery of the mechanism of immune activation by bacterial DNA, it may be concluded that the use of synthetic oligonucleotides containing these CpG motifs would induce a similar pattern of immune activation, and would also be capable of causing tumor regression.

As discussed in the interview, prior to filing the instant application, clinical trials had been conducted with bacterial DNA that established the use of bacterial DNA in the treatment of cancer. For example, Tokunaga et al. (Jpn. J. Infect. Dis 52, 1-11, 1999), a review article attached, describes various clinical trials involving administration of bacterial DNA to humans that demonstrated positive effects in cancer patients. Bacterial DNA was found to be effective for various cancers including malignant lymphomas, squamous cell carcinoma, cutaneous lesions of adult T cell leukemia and intraepidermal

carcinomas (See page 5, item 7). Thus, as of the filing date, the skilled artisan recognized that bacterial DNA was useful in the treatment of cancer, even though the active component was unknown. In the present application, Applicant demonstrated that synthetic unmethylated CpG oligonucleotides mimicked bacterial DNA in inducing an immune response. … The Office Action suggests that Krieg (J. Clin Invest. 117, p. 1184, 2007) provides teachings demonstrating the unpredictability of the use of CpG oligonucleotides as a monotherapy for the treatment of cancer. Applicant respectfully disagrees and reiterates that the claims are not limited to monotherapy. The addition of other therapeutic agents is encompassed by the broadest claims. Further, claims 43, 44, 68, 72-73, and 79-80 all specifically recite the combination of a CpG ODN with a second therapeutic agent. Moreover, the overall teachings of Krieg (2007) support the therapeutic value of CpG oligonucleotides in the treatment of diseases such as cancer. Specifically, Krieg teaches that "In mice with relatively small tumors, up to a few millimeters in diameter, CpG monotherapy can be sufficient to induce T cell-mediated tumor regression", and "In human also, monotherapy with the TLR9 agonist CPG 7909 (now called PF-3512676 when used in oncology without a vaccine) or another B-class CpG ODN, 1018 ISS, activates NK cells and induces a Thl cytokine response in humans with B cell lymphomas." (Page 1190, first column, last paragraph). Table 2 and Table 3 provides a list of clinical trials, including phase I and phase II monotherapy using CpG oligonucleotides. When read in its entirety Krieg is supportive of the predictability of the claimed invention. … The Examiner also cited Agrawal et al (Trends in Mol Med. 2002, 8:114-121) as teaching that different effects are observed

with different CpG ODNs, and Crooke et al. (Therapeutic application of Nucleotides, R.G. Landers Co., Austin, TX, 1995) as teaching that phosphorothioate nucleotides clearly have significant limits. CpG ODN may produce variant results, with some ODNs producing more potent immune stimulation and others preferentially activating certain subsets of immune cells. However, as described in the specification, Applicant established that CpG oligonucleotides, as a class of molecules, produce an immune response that collectively is useful in the treatment of disease. Miscellaneous statements in the references cited by the Office referring to future work, fine-tuning, optimization or additional experimentation to prove clinical efficacy do not support a finding of lack of enablement for the claimed invention. While the statements may suggest that-as with any drug being developed-further experimentation is required to further develop certain aspects of the drug, they do not support the finding that such experimentation is undue with respect to the invention as claimed. In any event, they do not outweigh the direct and most pertinent evidence of enablement presented by Applicant (see response pages 6-11).

Response to Arguments

In response to these arguments, as set forth in a previous office action, the specification discloses the immunostimulatory activity of oligonucleotides containing an unmethylated CpG dinucleotide. However, such disclosure does not enable a skilled artisan to treat just any cancer comprising administering oligonucleotides containing an unmethylated CpG dinucleotide. The state of the art at the time of filing is such that there is a high degree of unpredictability in the treatment of cancers comprising

administering oligonucleotides containing an unmethylated CpG dinucleotide. The claims are drawn to a method of treatment of just any cancer comprising a huge genus of oligonucleotides containing an unmethylated CpG dinucleotide. In view of the unpredictability in the art, with regard to the treatment of cancers, one of ordinary skill in art would require an undue experimentation to practice the claimed method with all the oligonucleotides encompassed within the claims for all the different types of cancers. Further, the claims require administering an effective amount of the oligonucleotides ranging from 8 to 100 nucleotides. Thus, the process of achieving a desirable effective amount for administration in vivo for each and every one of the oligonucleotides encompassed within the huge genus of oligonucleotides encompassed by the claims is a very lengthy and complicated process; because, the prior art recognizes that unlike the situation in vitro, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist in vitro. Therefore, prediction of drug effects in cancer patients based solely on in vitro data is not reliable and further evaluation in animal tumor systems is essential. (Zips, et al. In Vivo, 2005, as cited on the PTO-892 mailed February 7, 2007). Specifically addressing the treatment of cancer at the time of filing, Tokunaga, et al. (Japanese Journal of Infectious Disease, 1999, as cited in applicant's arguments) administers BCG DNA for the treatment of skin cancers. Even if the BGC DNA were identical to the instantly claimed CpG DNA (which the examiner is not implying), the treatment of skin cancers would not

be sufficient to enable the treatment of all cancers with the same BCG DNA. Each of the clinical trial references cited by applicant are well after the instant filing date. As set forth in a previous office action, most of these references administer the CpG DNA in combination with an additional agent. While the claims are not limited to monotherapy, when given the broadest reasonable interpretation, the claims read on monotherapy of a broad range of CpG DNA molecules for the treatment of just any cancer. At the time of filing, one of ordinary skill in the art would have been required to do undue experimentation do determine which CpG DNA molecules, if any, would be effective as a monotherapy to treat just any cancer. Regarding the combination therapy, at the time of filing, one of ordinary skill in the art would have possibly been able to administer CpG DNA molecules for the treatment of skin cancers based on the teachings of Tokunaga, et al., but would not have extrapolated that data to just any cancer type.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In deciding In re Fisher, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001, 1005 (CA FC 1997).

Supporting documents cannot be relied upon to correct the deficiencies of the

specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. MPEP 2164.05(a) states that if individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Hence, as stated in the previous office actions, the studies published well after the filing date of the instant application clearly recognize the obstacles in treating cancers comprising oligonucleotides containing an unmethylated CpG dinucleotide and address the unpredictability.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

Conclusion

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
December 28, 2010

/Anne M. Gussow/
Primary Examiner, Art Unit 1643